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14. ABSTRACT <p>Background. A large proportion of patients with amnesic mild cognitive impairment (MCI) convert to Alzheimer's disease (AD) and hence acetylcholinesterase inhibitors (AChEI) are commonly prescribed in patients with MCI though it is not FDA approved for this condition. Therefore, predicting which MCI patients are likely to improve cognitively with AChEI treatment is important.</p> <p>Hypotheses. 1. The acute decrease in UPSIT (Odor identification test) scores from pre- to post- atropine nasal spray challenge conducted at baseline (0 weeks) will be associated with cognitive improvement (SRT total recall and modified ADAS-cog) from baseline to 24 weeks and 52 weeks of donepezil treatment. 2. Increase in UPSIT scores from baseline to 8 weeks of donepezil treatment will be associated with cognitive improvement from baseline to 24 and 52 weeks.</p> <p>Exploratory Hypothesis. The acute atropine-induced decrease in UPSIT scores, and increase in UPSIT scores from baseline to 8 weeks, will be associated with a decreased likelihood of conversion to dementia at 52 weeks.</p> <p>Study Design. In this proof of concept study, 60 patients with mild cognitive impairment will be treated openly with donepezil 5 to 10 mg per day and followed for 52 weeks (one year), with an atropine challenge test also conducted at baseline.</p>					
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Table of Contents

Introduction.....	4
Body.....	4
Key Research Accomplishments.....	7
Reportable Outcomes.....	7
Conclusion.....	7
References.....	N/A

INTRODUCTION: Individuals with cognitive deficits, whether due to traumatic brain injury or due to mild cognitive impairment, may improve with donepezil treatment. Olfactory identification deficits may be an early test that can identify who in the high-risk population is most likely to develop dementia and therefore identifies patients for early interventions. Based on the study results, the presence of olfactory identification deficits can be used to decide if the patient should receive treatment with a cholinesterase inhibitor like donepezil.

BODY: Thirteen patients have been recruited and are currently participating in the study. Of the 13 active patients, 5 are female and 8 are male. The mean age of the patients is 73.15, standard deviation 8.06. Eleven of thirteen active patients (12th and 13th patients were recruited very recently and have not yet completed the atropine challenge and not yet started donepezil) have been given baseline pre and post atropine spray UPSITs, have completed all procedures accordingly to the protocol schedule, and have been treated with either 5mg or 10mg Donepezil daily. Two patients could not tolerate donepezil 5 mg daily and comparable cholinesterase inhibitors, galantamine and rivastigmine, were used instead of donepezil after obtaining IRB approval (explained below). Minor modifications have been made since the start of this study: (1) the neuropsychological inclusion/exclusion criteria were modified. The updated Wechsler Memory Scale-III Logical Memory subtests has replaced the WMS-R Logical Memory subtests. The Free and Cued Selective Reminding Test (FC-SRT) immediate recall and delayed recall has been added. The Selective Reminding Test (SRT) immediate and delayed recall has been added. A patient qualifies for the study if he/she scores greater than 1.5 SD below norms on at least one of the three measures. The rationale for the change is to improve recruitment. There is considerable variability among patients when they do different tests of memory, even on the same day. Further, the measures assess different memory functions (WMS-III Logical Memory focuses on paragraph recall whereas the SRT and FC-SRT focus on free and/or cued recall of word lists). In addition, the manner in which norms were derived for the two tests was very different. Therefore, including patients who score poorly on either test is valid and will improve recruitment. The SRT and FC-SRT are very similar (the FC-SRT is a derived, abbreviated version of the FC-SRT), however we have come across several cases in which subjects are recruited shortly after completing the full SRT either for clinical diagnostic testing or in other research studies. Repeating the FC-SRT when we recruit these patients may produce inaccurate results because of practice effects when identical or very similar tests are repeated after only a short interval. Therefore, when these patients take the SRT within three months prior to the start of our study and score at least 1.5 SD below norms, we can use that score for the patient to meet inclusion criteria; (2) the medication inclusion criteria were also modified. Patients can now be started on galantamine or rivastigmine, alternative cholinesterase inhibitors, if they could not tolerate donepezil in the past. The three medications are all cholinesterase inhibitors and are essentially identical in their efficacy in studies of Alzheimer's disease, and the only differences are minor differences in side effects. This exemption has helped to increase recruitment for the study. In addition, we are in the process of submitting an additional protocol modification to the IRB. We have screened 29 subjects. 15 subjects were eligible, and 14 were not eligible. Of the 15 who were eligible, 13 have enrolled to date. Of the 14 who were ineligible, 8 were ineligible because they were already on cholinesterase inhibitors or memantine (2 subjects were on memantine and donepezil; 2 subjects were on memantine and rivastigmine; 1 subject was on memantine; 3 subjects were on donepezil).

Recruitment Log

Time Point	Screened	Recruited	Ineligible due to AChEI/Memantine
Quarter 1	0	0	N/A
Quarter 2	4	3	0
Quarter 3	7	2	5
Quarter 4	18	8	3

As noted above, many of the subjects were not eligible for the study because they were already on cholinesterase inhibitors or memantine, prescribed by their physicians, often primary care physicians. In many cases, they were started on these medications without systematic cognitive testing and assessment, and the diagnosis was unclear. Therefore, if the patient is otherwise eligible for study participation, we will recruit the patient on cholinesterase inhibitors or memantine and who will then undergo a two-week wash-out (if they agree to do this) before starting all study procedures. The atropine challenge takes place on a single day and donepezil can be started immediately after the completion of the procedure. Therefore, the total delay before starting donepezil will be 2 weeks (the wash-out period). This modification should help considerably with recruitment; (3) the atropine spray challenge procedure posed difficulties at first, but the issue has now been resolved. Intranasal Atropine has been administered to the first eleven subjects who signed consent (the 12th and 13th patients recently signed consent and the procedure will be done in the next week). Initially, the planned standard procedure was to administer the full 40-item University of Pennsylvania Smell Identification Test (UPSIT). Immediately after the UPSIT, a 1 mg atropine nasal spray (0.5 mg per nostril) was administered. The patient then assumed the “Mecca” position for 1 minute to ensure that the atropine reached the top of the nasal cavity in close proximity to the cribriform plate. Another 45 minutes were allowed to lapse in order to obtain the full anticholinergic effect of atropine, and then the UPSIT was again administered. In the first several patients, we needed to refine and improve the IN atropine delivery, and its effect on UPSIT performance was monitored closely. We now have a reliable and consistent procedure that we believe will be able to answer the primary hypothesis of this project. The process to get to this point involved several steps. In the first five subjects there was little change in the UPSIT (olfaction test) from pre-IN atropine challenge to post-IN atropine challenge. These subjects had IN atropine delivered as a “nasal spray” via an atomizer, a device attached to a 1 cc syringe typically used to deliver adrenaline in the pediatric ER. The experience is similar to the experience of using a metered dispenser inhaler or a “puff” of atropine in the nose. In the first three subjects, we delivered a 0.05 cc puff of atropine (0.5 mg) into each nostril and in the next two subjects we delivered a 0.1 cc (1 mg) puff into one nostril. Immediately after the atropine was delivered, the subject assumed the Mecca position on the floor for one minute, and after another 45 minutes, the UPSIT was again administered. Since neither half the dose of IN atropine puffed into each nostril nor the full IN dose of atropine puffed into one nostril had any demonstrable effect on the post-challenge UPSIT score that was similar to the pre-atropine score, we had several conversations via email and an in person meeting with Dr. Peter Schofield from Australia, when he was in town, to discuss what was different between his technique (he pioneered this atropine challenge technique to assess impact on olfactory identification) and ours. We concluded that the atomizer may be producing droplets that are too fine, and that the atropine is either getting filtered out before reaching the cribriform plate or the puffer delivery system was just not delivering a strong enough spray to reach the upper nasal cavity. At Dr. Peter Schofield’s suggestion, we tried the modified “nasal dropper” method, in which the total volume of atropine (0.1 cc) was administered in total, in one nostril, via a one-cc syringe. This was immediately followed

by the standard 1 minute Mecca position, 45 minute delay, and repeat UPSIT test, as before. In the next 3 subjects, this method produced a similar set of mixed results. Little, if any, decrease was seen from the pre-IN atropine challenge UPSIT to the post-IN atropine challenge UPSIT. For the most recent 3 subjects, we have adopted a different IN atropine delivery process, called the “squirt system”, developed by Scheibe & colleagues in 2008. The squirt system includes a 2 cm sterile plastic tube attached to a one cc syringe. The syringe is filled with 0.1 cc of atropine and then the tube is placed in the nasal cavity parallel to the nasal septum, and directed at the nasal cleft (back and up towards the cribriform plate). The atropine is then squirted up towards the superior turbinate bone in the nose. This is immediately followed by the standard 1 minute Mecca position, 45 minute delay, and repeat UPSIT test, as before. As shown in the last 3 subjects in the table below, this approach is yielding consistent decreases in UPSIT scores (7, 5, and 4 points respectively on the 40-point UPSIT) after the IN atropine.

PATIENT	PRE-ATROPINE UPSIT SCORE	POST-ATROPINE UPSIT SCORE
101	33	32
102	35	36
103	30	31
104	35	33
105	28	28
106	24	24
107	24	31
108	17	18
109	35	28
110	25	20
112	33	29

Henceforth, we plan to use the squirt method only and will continue to monitor its effects and ensure that the effect seen in the last 3 subjects is maintained in subsequent subjects. If it is not maintained, we will re-evaluate the procedure again. From a data analytic standpoint, we will first include all subjects in evaluating the change in UPSIT from pre- to post-atropine spray as a predictor of donepezil treatment response, and then separately assess the impact of the first 8 subjects where different techniques were used as noted above. We will include and then exclude the subset of the first 8 patients in statistical analyses and then assess if the results change. Of note, the atropine challenge-induced change in UPSIT scores represents the first of the two main hypotheses; the second hypothesis pertaining to change in UPSIT scores from baseline to 8 weeks as a predictor of longer-term donepezil response is unaffected by the change in the atropine spray challenge procedure.

KEY RESEARCH ACCOMPLISHMENTS: No presentations or publications to date from this study.

REPORTABLE OUTCOMES: None; study is not yet complete.

CONCLUSIONS

We are actively recruiting for this study from the sources described in the original grant application and expect to increase recruitment further with the proposed IRB modification and increased advertising efforts both in print media and the internet.

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Scheibe M, Bethge C, Witt M, Hummel T. Intranasal administration of drugs. Arch Otolaryngol Head Neck Surg. 2008 Jun;134(6):643-6. doi: 10.1001/archotol.134.6.643.

APPENDICES:

None.